Public Assessment Report

Decentralised Procedure

Isotretinoin 5 mg Soft Capsules
Isotretinoin 10 mg Soft Capsules
Isotretinoin 20 mg Soft Capsules
Isotretinoin 40 mg Soft Capsules

(isotretinoin)

UK/H/3577/001-4/DC
UK licence numbers: PL 17871/0100-3

Jenson Pharmaceutical Services Ltd
LAY SUMMARY

On 13th September 2011, the MHRA granted Jenson Pharmaceutical Services Ltd Marketing Authorisations (licences) for the medicinal products Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules (PL 17871/0100-3). These are prescription-only medicines (POM).

Isotretinoin is a medicine related to vitamin A. It is used to treat severe types of acne that can cause permanent scarring, which has not improved after other anti-acne treatments. Isotretinoin can only be prescribed by a doctor who has specialised in the treatment of severe acne.

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

### Information about Initial Procedure

| Product Name | Isotretinoin 5 mg Soft Capsules  
|              | Isotretinoin 10 mg Soft Capsules  
|              | Isotretinoin 20 mg Soft Capsules  
|              | Isotretinoin 40 mg Soft Capsules |
| Type of Application | Generic, Article 10.1 – 5 mg, 10 mg and 20 mg strengths  
|                    | Hybrid, Article 10.3 – 40 mg strength |
| Active Substance | Isotretinoin |
| Form | Soft capsules |
| Strength | 5 mg, 10 mg, 20 mg, 40 mg |
| MA Holder | Jenson Pharmaceutical Services Ltd  
|           | Carradine House  
|           | 237 Regents Park Road  
|           | London  
|           | N3 3LF |
| Reference Member State (RMS) | UK |
| Concerned Member States (CMS) | UK/H/3577/001 & 004/DC: Belgium, Italy, Poland, Portugal and Spain  
|                               | UK/H/3577/002 & 003/DC: Belgium, Italy, Poland |
| Procedure Number | UK/H/3577/001-4/DC |
| Timetable | End of Procedure: Day 210 – 3rd August 2011 |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules (PL 17871/0100-3) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

- Isotretinoin 5 mg Soft Capsules
- Isotretinoin 10 mg Soft Capsules
- Isotretinoin 20 mg Soft Capsules
- Isotretinoin 40 mg Soft Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains isotretinoin 5/10/20/40 mg.

Excipient(s):
- Soya Oil: 52.1/104.2/208.4/191.5 mg/capsule

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

- Each oval capsule has a bi-coloured opaque red/brown and cream shell with a bright yellow/orange fill and is printed on one side with the logo “5”
- Each oval capsule has an opaque red/brown shell with a bright yellow/orange fill and is printed on one side with the logo “I 10”
- Each oval capsule has a bi-coloured opaque red/brown and cream shell with a bright yellow/orange fill and is printed on one side with the logo “I 20”
- Each oval capsule has an opaque orange/brown shell with a bright orange/yellow fill and is printed on one side with the logo “I 40”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy

4.2 Posology and method of administration

Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

The capsules should be taken with food once or twice daily.

Adults including adolescents and the elderly:

Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5-1.0 mg/kg per day.

Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to
be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-24 weeks is normally sufficient to achieve remission.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose. As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.

**Patients with severe renal insufficiency:**
In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4).

**Children**
Isotretinoin is not indicated for the treatment of prepubertal acne and is not recommended in patients less than 12 years of age due to a lack of data on efficacy and safety.

**Patients with intolerance**
In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

### 4.3 Contraindications

Isotretinoin is contraindicated in women who are pregnant or breastfeeding (see section 4.6).

Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4).

Isotretinoin is also contraindicated in patients
- With hepatic insufficiency
- With excessively elevated blood lipid values
- With hypervitaminosis A
- With hypersensitivity to isotretinoin or to any of the excipients
- Receiving concomitant treatment with tetracyclines (see section 4.5)
- Allergic to peanut or soya oil as isotretinoin contains soya-bean oil

### 4.4 Special warnings and precautions for use

**Pregnancy Prevention Programme**

This medicinal product is TERATOGENIC

Isotretinoin is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- She has severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy (see section 4.1).
- She understands the teratogenic risk.
- She understands the need for rigorous follow-up, on a monthly basis.
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the duration of treatment and 1 month after the end of treatment. At least one and preferably two complementary forms of contraception including a barrier method should be used.
- Even if she has amenorrhoea she must follow all of the advice on effective contraception.
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
She understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment.

She has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.
- The patient has used at least one and preferably two methods of effective contraception including a barrier method for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment.
- Negative pregnancy test results have been obtained before, during and 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented.

**Contraception**

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception.

As a minimum requirement, female patients at potential risk of pregnancy must use at least one effective method of contraception. Preferably the patient should use two complementary forms of contraception including a barrier method. Contraception should be continued for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhoea.

**Pregnancy testing**

According to local practice medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL are recommended to be performed in the first 3 days of the menstrual cycle, as follows.

**Prior to starting therapy:**

In order to exclude the possibility of pregnancy prior to starting contraception, it is recommended that an initial medically supervised pregnancy test should be performed and its date and result recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception.

A medically supervised pregnancy test should also be performed during the consultation when isotretinoin is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. This test should ensure the patient is not pregnant when she starts treatment with isotretinoin.

**Follow-up visits**

Follow-up visits should be arranged at 28 day intervals. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient’s sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhoea). Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

**End of treatment**

Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

**Prescribing and dispensing restrictions**

Prescriptions of isotretinoin for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of isotretinoin should occur on the same day. Dispensing of isotretinoin should occur within a maximum of 7 days of the prescription.
Male patients
The available data suggest that the level of maternal exposure from the semen and seminal fluid of the patients receiving isotretinoin, is not of a sufficient magnitude to be associated with the teratogenic effects of isotretinoin.

Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month following discontinuation of isotretinoin because of the potential risk to the fetus of a pregnant transfusion recipient.

Educational material
In order to assist prescribers, pharmacists and patients in avoiding fetal exposure to isotretinoin the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of isotretinoin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Psychiatric disorders
Depression including aggravation of pre-existing depression, anxiety, aggressive tendencies, mood alterations, psychotic symptoms and, very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Skin and subcutaneous tissues disorders
Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7-10 days, and usually does not require dose adjustment.

Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on isotretinoin for a period of 5-6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and more rarely post inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping.

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase.

Patients should be advised to use a skin moisturising ointment or cream and a lip balm from the start of treatment as isotretinoin is likely to cause dryness of the skin and lips.

There have been post-marketing reports of severe skin reactions (e.g. erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) associated with isotretinoin use. As these events may be difficult to distinguish from other skin reactions that may occur (see section 4.8), patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If a severe skin reaction is suspected, isotretinoin treatment should be discontinued.

Eye disorders
Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application
of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Decreased night vision has also been reported and the onset in some patients was sudden (see section 4.7). Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin may be necessary.

Musculo-skeletal and connective tissue disorders
Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin, particularly in those undertaking vigorous physical activity (see section 4.8).

Bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments have occurred after several years of administration at very high doses for treating disorders of keratinisation. The dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne.

Benign intracranial hypertension
Cases of benign intracranial hypertension have been reported, some of which involved concomitant use of tetracyclines (see sections 4.3 and 4.5). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.

Hepatobiliary disorders
Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Transient and reversible increases in liver transaminases have been reported. In many cases these changes have been within the normal range and values have returned to baseline levels during treatment. However, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

Renal insufficiency
Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin can be given to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose (see section 4.2).

Lipid Metabolism
Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Elevated serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment and may also respond to dietary measures.

Isotretinoin has been associated with an increase in plasma triglyceride levels. Isotretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8). Levels in excess of 800 mg/dL or 9 mmol/L are sometimes associated with acute pancreatitis, which may be fatal.

Gastrointestinal disorders
Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (haemorrhagic) diarrhoea should discontinue isotretinoin immediately.

Allergic reactions
Anaphylactic reactions have been rarely reported, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

High Risk Patients
In patients with diabetes, obesity, alcoholism or a lipid metabolism disorder undergoing treatment with isotretinoin, more frequent checks of serum values for lipids and/or blood glucose may be necessary. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy.
4.5 Interaction with other medicinal products and other forms of interaction

Patients should not take vitamin A as concurrent medication due to the risk of developing hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumour cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see section 4.3 and section 4.4).

Concurrent administration of isotretinoin with topical keratolytic or exfoliate anti-acne agents should be avoided as local irritation may increase (see section 4.4).

4.6 Fertility, Pregnancy and lactation

Pregnancy is an absolute contraindication to treatment with isotretinoin (see section 4.3). If pregnancy does occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe and serious malformation of the fetus.

The fetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.

If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Lactation:
Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the child exposed via mothers' milk, the use of isotretinoin is contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines

A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy (see section 4.4 and section 4.8). Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

Drowsiness, dizziness and visual disturbances have been reported very rarely. Patients should be warned that if they experience these effects, they should not drive, operate machinery or take part in any other activities where the symptoms could put either themselves or others at risk.

4.8 Undesirable effects

The following symptoms are the most commonly reported undesirable effects with isotretinoin: dryness of the mucosa e.g. of the lips, cheilitis, the nasal mucosa, epistaxis, and the eyes, conjunctivitis, dryness of the skin. Some of the side effects associated with the use of isotretinoin are dose-related. The side effects are generally reversible after altering the dose or discontinuation of treatment, however some may persist after treatment has stopped.

<table>
<thead>
<tr>
<th>Infections:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Gram positive (mucocutaneous) bacterial infection</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders:</td>
<td></td>
</tr>
<tr>
<td>Very common (≥1/10)</td>
<td>Anaemia, Red blood cell sedimentation rate increased, Thrombocytopenia, Thrombocytosis</td>
</tr>
<tr>
<td>Common (≥1/100, &lt;1/10)</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Immune system disorders:</td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10 000, &lt;1/1000)</td>
<td>Allergic skin reaction, Anaphylactic reactions, Hypersensitivity</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders:</td>
<td></td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Diabetes mellitus, Hyperuricaemia</td>
</tr>
</tbody>
</table>
### PAR Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules

**Psychiatric disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare (≥1/10,000, &lt;1/1000)</td>
<td>Depression including aggravation of pre-existing depression, Aggressive tendencies, Anxiety, Mood Alterations</td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Abnormal behaviour, Psychotic disorder, Suicidal ideation, Suicide attempt, Suicide</td>
</tr>
</tbody>
</table>

**Nervous system disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common (≥1/100, &lt;1/10)</td>
<td>Headache</td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Benign intracranial hypertension, Convulsions, Drowsiness, Dizziness</td>
</tr>
</tbody>
</table>

**Eye disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥1/10)</td>
<td>Blepharitis, Conjunctivitis, Dry eye, Eye irritation</td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Blurred vision, Cataract, Colour blindness (colour vision deficiencies), Contact lens intolerance, Corneal opacity, Decreased night vision, Keratitis, Papilloedema (as sign of benign intracranial hypertension), Photophobia, Visual disturbances</td>
</tr>
</tbody>
</table>

**Ear and labyrinth disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Hearing impaired</td>
</tr>
</tbody>
</table>

**Vascular disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Vasculitis (for example Wegener’s granulomatosis, allergic vasculitis)</td>
</tr>
</tbody>
</table>

**Respiratory, thoracic and mediastinal disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common (≥1/100, &lt;1/10)</td>
<td>Epistaxis, Nasal dryness, Nasopharyngitis</td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Bronchospasm (particularly in patients with asthma), Hoarseness</td>
</tr>
</tbody>
</table>

**Gastrointestinal disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Colitis, Ileitis, Dry throat, Gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, Nausea, Pancreatitis (see section 4.4)</td>
</tr>
</tbody>
</table>

**Hepatobiliary disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥1/10)</td>
<td>Transaminase increased (see section 4.4)</td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

**Skin and subcutaneous tissues disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥1/10)</td>
<td>Cheilitis, Dermatitis, Dry skin, Localised exfoliation, Pruritus, Rash erythematous, Skin fragility (and risk of frictional trauma)</td>
</tr>
<tr>
<td>Rare (≥1/10,000, &lt;1/1000)</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Acne fulminans, Acne aggravated (acne flare), Erythema (facial), Exanthema, Hair disorders, Hirsutism, Nail dystrophy, Paronychia, Photosensitivity reaction, Pyogenic granuloma, Skin hyperpigmentation, Sweating increased</td>
</tr>
<tr>
<td>Unknown (1)</td>
<td>Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis.</td>
</tr>
</tbody>
</table>

**Musculo-skeletal and connective tissue disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥1/10)</td>
<td>Arthralgia, Myalgia, Back pain (particularly in children and adolescent patients)</td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Arthritis, Calcinoisis (calcification of ligaments and tendons), Epiphyses premature fusion, Exostosis, (hyperostosis), Reduced bone density, Tendonitis</td>
</tr>
</tbody>
</table>

**Renal and urinary disorders:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Glomerulonephritis</td>
</tr>
</tbody>
</table>

**General disorders and administration site conditions:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Granulation tissue (increased formation of), Malaise</td>
</tr>
</tbody>
</table>

**Investigations:**

<table>
<thead>
<tr>
<th>Rarity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥1/10)</td>
<td>Blood triglycerides increased, High density lipoprotein decreased</td>
</tr>
<tr>
<td>Common (≥1/100, &lt;1/10)</td>
<td>Blood cholesterol increased, Blood glucose increased, Haematuria, Proteinuria,</td>
</tr>
<tr>
<td>Very Rare (≤1/10,000)</td>
<td>Blood creatine phosphokinase increased</td>
</tr>
</tbody>
</table>

1. cannot be estimated from the available data

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The incidence of the adverse events was calculated from pooled clinical trial data involving 824 patients and from post-marketing data.
4.9 Overdose

Isotretinoin is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar. These symptoms would be expected to be reversible and to subside without the need for treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Retinoid for the treatment of acne

ATC code: D10BA01

Mechanism of action
Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

Efficacy
Hypercornification of the epithelial lining of the pilosebaceous unit leads to shedding of corneocytes into the duct and blockage by keratin and excess sebum. This is followed by formation of a comedone and, eventually, inflammatory lesions. Isotretinoin inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly programme of differentiation. Sebum is a major substrate for the growth of Propionibacterium acnes so that reduced sebum production inhibits bacterial colonisation of the duct.

5.2 Pharmacokinetic properties

Absorption
The absorption of isotretinoin from the gastro-intestinal tract is variable and dose-linear over the therapeutic range. The absolute bioavailability of isotretinoin has not been determined, since the compound is not available as an intravenous preparation for human use, but extrapolation from dog studies would suggest a fairly low and variable systemic bioavailability. When isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions.

Distribution
Isotretinoin is extensively bound to plasma proteins, mainly albumin (99.9%). The volume of distribution of isotretinoin in man has not been determined since isotretinoin is not available as an intravenous preparation for human use. In humans little information is available on the distribution of isotretinoin into tissue. Concentrations of isotretinoin in the epidermis are only half of those in serum. Plasma concentrations of isotretinoin are about 1.7 times those of whole blood due to poor penetration of isotretinoin into red blood cells.

Metabolism
After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin (all-trans retinoic acid), and 4-oxo-tretinoin. These metabolites have shown biological activity in several in vitro tests. 4-oxo-isotretinoin has been shown in a clinical study to be a significant contributor to the activity of isotretinoin (reduction in sebum excretion rate despite no effect on plasma levels of isotretinoin and tretinoin). Other minor metabolites includes glucuronide conjugates. The major metabolite is 4-oxo-isotretinoin with plasma concentrations at steady state, that are 2.5 times higher than those of the parent compound.

Isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised (interconverted), and the metabolism of tretinoin is therefore linked with that of isotretinoin. It has been estimated that 20-30% of an isotretinoin dose is metabolised by isomerisation.

Enterohepatic circulation may play a significant role in the pharmacokinetics of isotretinoin in man. In vitro metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo-isotretinoin and tretinoin. No single isoform appears to have a predominant role. Isotretinoin and its metabolites do not significantly affect CYP activity.
Elimination
After oral administration of radiolabelled isotretinoin approximately equal fractions of the dose were recovered in urine and faeces. Following oral administration of isotretinoin, the terminal elimination half-life of unchanged drug in patients with acne has a mean value of 19 hours. The terminal elimination half-life of 4-oxo-isotretinoin is longer, with a mean value of 29 hours.

Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of isotretinoin therapy.

Pharmacokinetics in special populations
Since isotretinoin is contraindicated in patients with hepatic impairment, limited information on the kinetics of isotretinoin is available in this patient population. Renal failure does not significantly reduce the plasma clearance of isotretinoin or 4-oxo-isotretinoin.

5.3 Preclinical safety data

Acute toxicity
The acute oral toxicity of isotretinoin was determined in various animal species. LD50 is approximately 2000 mg/kg in rabbits, approximately 3000 mg/kg in mice, and over 4000 mg/kg in rats.

Chronic toxicity
A long-term study in rats over 2 years (isotretinoin dosage 2, 8 and 32 mg/kg/d) produced evidence of partial hair loss and elevated plasma triglycerides in the higher dose groups. The side effect spectrum of isotretinoin in the rodent thus closely resembles that of vitamin A, but does not include the massive tissue and organ calcifications observed with vitamin A in the rat. The liver cell changes observed with vitamin A did not occur with isotretinoin.

All observed side effects of hypervitaminosis A syndrome were spontaneously reversible after withdrawal of isotretinoin. Even experimental animals in a poor general state had largely recovered within 1-2 weeks.

Teratogenicity
Like other vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenic and embryotoxic.

Due to the teratogenic potential of isotretinoin there are therapeutic consequences for the administration to women of a childbearing age (see section 4.3, section 4.4 and section 4.6).

Fertility
Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin.

Mutagenicity
Isotretinoin has not been shown to be mutagenic nor carcinogenic in in vitro or in vivo animal tests respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Soya-bean oil, refined
Beeswax, yellow
Hydrogenated vegetable oil (derived from soya-bean oil)

Capsule shell
Glycerol
Gelatin
Purified water
Red iron oxide (E172)
Lecithin
Medium chain triglycerides

Additionally for 5 mg, 20 mg and 40 mg strength (PL 17871/0100, 0102, 0103) only:
Yellow iron oxide (E172)
Titanium dioxide (E171)
Ribbon print solvent
Components of Ribbon print solvent
Purified water
Ethanol

Black ink
Components of black printing ink
SDA 35 alcohol
Propylene glycol
Black iron oxide
Polyvinyl acetate phthalate
Purified water
Isopropyl alcohol
Macrogol/PEG 400
Ammonium hydroxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
For 5 mg strength (PL 17871/0100):
30 months
For 10 mg, 20 mg, 40 mg strengths (PL 17871/0101-3):
3 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container. Keep the container tightly closed to protect from light.

6.5 Nature and contents of container
Thermoform blister. Each blister strip is formed from opaque white triplex laminate (PVC/PE/PVdC), sealed with aluminium lidding foil.

Pack sizes of 30, 50 and 100. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special instructions.

7 MARKETING AUTHORISATION HOLDER
Jenson Pharmaceutical Services Ltd
Carradine House
237 Regents Park Road
London
N3 3LF

8 MARKETING AUTHORISATION NUMBER(S)
PL 17871/0100
PL 17871/0101
PL 17871/0102
PL 17871/0103

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/09/2011

10 DATE OF REVISION OF THE TEXT
13/09/2011
Module 3

Patient Information Leaflet – text version

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

PACKAGE LEAFLET: INFORMATION FOR THE USER

ISOTRETINOIN 5 mg, 10 mg, 20 mg, 40 mg SOFT CAPSULES (Isotretinoin)

Read all of this leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need to read it again.

If you have further questions, please ask your doctor or your pharmacist.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1 – What Isotretinoin is and what it is used for
2 – Before you take Isotretinoin
3 – How to take Isotretinoin
4 – Possible side effects
5 – How to store Isotretinoin
6 – Further information

1. WHAT ISOTRETINOIN IS AND WHAT IT IS USED FOR

These capsules contain isotretinoin, which is a medicine related to vitamin A.

Isotretinoin is used to treat severe types of acne that can cause permanent scarring, which has not improved after other anti-acne treatments.

Isotretinoin can only be prescribed by a doctor who has specialised in the treatment of severe acne.

2. BEFORE YOU TAKE ISOTRETINOIN

Do not take Isotretinoin - if you:

- are pregnant, think you may be pregnant or are planning a pregnancy
- are of a child-bearing age and you are not following the Pregnancy Prevention Plan (see box “Pregnancy and breast-feeding: important” below)
- are breast-feeding
- are allergic (hypersensitive) to isotretinoin, or allergic to peanuts or soya (Isotretinoin contains soya oil) or any of the other capsule ingredients
- are taking certain antibiotics called tetracyclines
- are younger than 12 years of age
- have a severe liver disease
- have a high level of vitamin A level in your body
- have a high level of cholesterol or triglycerides in your blood

Please tell your doctor if any of the above statements apply to you.
Take special care with Isotretinoin - tell your doctor if:

- you have or have had depression or other mental health problems including previous experience of suicidal behaviour
- you have problems with your kidneys or your liver
- you are overweight
- you regularly drink a lot of alcohol
- you have diabetes, check your blood glucose levels more closely throughout the period of treatment
- you experience dryness of the skin or lips - you can apply moisturising ointments or creams to your skin and use a lip balm to reduce this effect
- your acne suddenly gets much worse - this usually occurs within 7 to 10 days, and usually does not require dose adjustment
- you are allergic to peanuts or soya.

Before, during and after treatment you will have regular blood tests to check that there are no changes to your kidneys, liver, cholesterol, and blood sugar levels. If there are changes, your doctor may decide to reduce the dose or stop treatment.

Avoid exposure to the sun as much as possible, and do not use sun lamps and UV beds completely. If exposure to the sun is unavoidable, use a sunscreen of at least SPF 15.

Reduce the amount of intensive physical exercise as pain in your joints or muscles may sometimes occur as part of your treatment.

You may find that your skin has become dry and fragile. Avoid the use of cosmetic skin treatments, for example do not apply anything that irritates the skin, like peeling cream.

Avoid wax depilation and cosmetic procedures designed to smooth your skin, or to reduce scars or aging signs (for example dermabrasion or laser therapy) for at least 6 months after the end of treatment. These procedures may cause skin scarring, colour changes or peeling of the skin.

Your eyes may become sensitive and dry throughout the treatment. Wear glasses rather than contact lenses. You may need to wear sunglasses to protect your eyes from being dazzled.
Pregnancy and breast-feeding, important:
Isotretinoin may cause serious damage (malformations, such as a large head or no ears) to your unborn child if you become pregnant during treatment or during the 5 weeks after the end of treatment. This drug may also cause a miscarriage.

You must not take Isotretinoin if:
- you are pregnant or if you intend to be pregnant during your treatment or up to 5 weeks after treatment ends
- you are breast-feeding. The medicine is likely to pass into your milk and may harm your baby.

Before starting treatment women of child-bearing age must discuss and agree to the following points with the doctor:
- you have understood why you must not become pregnant
- you have received a pregnancy prevention brochure
- you have agreed to use at least one effective method of contraception, and preferably two, including a barrier method (condom or cap):
  * at least 1 month before starting treatment
  * during ongoing treatment
  * for 5 weeks after treatment ends.
- you must use contraception even if you are not sexually active or if you do not have menstrual periods
- you understand and agree the need for monthly follow-up visits and for medically supervised pregnancy tests:
  * 1 month before starting treatment. The test is conducted during the first 3 days of the menstrual cycle (period)
  * each month during the treatment
  * 5 weeks after stopping it.

The result of each test must be negative: You must not become pregnant at any time during treatment or up to 5 weeks following the end of treatment.
- you must sign (yourself or the adult responsible for you) a consent form concerning treatment and contraception, confirming that:
  * you have been informed of the risks associated with Isotretinoin treatment
  * you agree to comply with the Pregnancy Prevention Plan.

Information for male patients-
Isotretinoin treatment does not damage sperm. Isotretinoin and its metabolites are present in very low levels in your sperm. These levels are too low to harm the unborn baby of your female partner.

You must remember not to share your medication with anyone, particularly not females.

Do not donate blood-
Do not donate blood during treatment and for 5 weeks after the end of treatment. If a pregnant woman were to receive your blood, her baby could be seriously damaged.

Taking other medicines-
Please tell your doctor or your pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
It is very important to tell your doctor if you are taking any medicine containing vitamin A.
Driving and using machines-
Be careful when driving or using machines at night because this treatment may affect your night vision. This can happen suddenly. It rarely continues once treatment has ended.

Important information about some ingredients of Isotretinoin-
This drug contains soya-bean oil. Do not take this medicine if you are allergic to peanuts or soya.

3. HOW TO TAKE ISOTRETINOIN

Always take Isotretinoin as your doctor has told you. You should check with your doctor or your pharmacist if you are not sure. Your dosage is calculated individually based on your body weight, and may be adjusted by your doctor during treatment.

The usual starting dose is 0.5 mg/kg per day, however your doctor will determine your individual requirements.

The capsules should be taken once or twice a day with food. Swallow the capsules whole without chewing or sucking them.

Normally treatment lasts from 16 to 24 weeks. You should always complete your course of treatment. Your skin may continue to improve for up to 8 weeks after the end of treatment. Most patients only need one course of treatment.

Your doctor will review your dose after a few weeks of treatment to determine if an adjustment is required. Doses are usually within the range of 0.5 - 1.0 mg/kg per day. If you have problems with your kidneys then your doctor will give you a lower dose.

If your doctor wishes you to have further treatment, you should wait for a period of 8 weeks before beginning a new course of treatment.

If you are not able to tolerate the recommended dose, your doctor will reduce the dose you receive, and your treatment will last longer.

If you take more Isotretinoin than you should-
If you have taken more capsules than you should, you may suffer from excessively high levels of vitamin A. The signs and symptoms include intense headaches, nausea or vomiting, sleepiness, irritability and itching. Contact your doctor, your pharmacist or the nearest hospital as soon as possible. Take the container and any remaining capsules with you.

If you forget to take Isotretinoin-
Skip the missed dose and take the next dose as normal. Do not take a double dose to make up for the forgotten dose.

If you have any further questions on the use of this product, ask your doctor or your pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Isotretinoin can cause side effects, although not everybody experiences these.

These are rare but serious side effects. If any of the following happen, stop taking Isotretinoin and tell your doctor or seek medical advice immediately:

• depression or worsening of depression (sadness, anxiety, becoming easily angered, aggression, irritability, loss of concentration, sleeping too much or too little, changes in weight or appetite, changes in mood or abnormal behaviour)
• thinking about harming yourself or thinking about committing suicide
any other side effect related to your mental health (such as hearing voices or seeing things that
not are there)
- persistent headache with nausea, vomiting or visual disorders, drowsiness. This may occur
commonly with certain antibiotics (tetracyclines)
- violent pain in the abdomen, with or without bloody diarrhoea, nausea and vomiting
- blurred vision or if you experience any difficulty in seeing
- severe allergic reaction (anaphylaxis) causing difficulty breathing, dizziness, collapse, shock,
severe itching and/or swelling.

The following are serious side effects occurring with unknown frequency:
- serious skin rashes (erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal
necrolysis), which are potentially life-threatening and require immediate medical attention.
These appear initially as circular patches often with central blisters usually on arms and hands
or legs and feet, more severe rashes may include blistering of the chest and back. Additional
symptoms such as infection of the eye (conjunctivitis) or ulcers of the mouth, throat or nose
may occur. Severe forms of rash may progress to widespread peeling of the skin which can be
life threatening. These serious skin rashes are often preceded by headache, fever, body aches
(flu-like symptoms). If you develop a rash or these skin symptoms, stop taking Isotretinoin
and contact your doctor immediately.

The others possible side effects are:

Very common (more than 1 in 10 patients):
- dry or chapped skin, particularly on the face and lips.
- red and fragile skin, rash or mild itching or mild shedding of skin or a combination of these
symptoms
- dryness of the eyes, redness or dried crusts
- eye irritation or conjunctivitis - causing itching and redness
- swelling of the eyelids
- back, muscle or joint pains
- you may bruise or bleed more easily
- change in liver function, which will be detected by blood tests given by your doctor
- looking pale, feeling unusually tired
- your blood tests show a decrease in high density lipoproteins (linked to cholesterol levels) or an
increase of blood triglycerides.

Common (less than 1 in 10 patients):
- headaches
- nasal dryness, nosebleeds
- symptoms of colds and flu, e.g. sore throat, runny nose, nasal congestion, sneezing and cough
- increased levels of blood glucose with thirst and increased urination
- increased levels of cholesterol (except HDL)
- presence of proteins or blood in the urine
- change in the number of white blood cells that can make you more prone to developing an
infection.

Rare (less than 1 in 1,000 patients):
- hair loss (your hair should become normal again when treatment is over).
- allergic skin reactions causing rash, itching, and swelling.
Very rare (less than 1 in 10,000 patients):

- sudden chest tightness and possible difficulty breathing (bronchospasm), particularly in patients with asthma
- dry throat which may cause hoarseness
- slight hearing loss
- inflammation of the kidneys: difficulty urinating or even inability to urinate together with swollen eyelids and severe tiredness
- increase levels of blood sugar
- high levels of uric acid in the blood
- increased levels of blood creatine phosphokinase
- dark urine, pale stools, yellowing of the eyes and the skin, nausea, fever and severe tiredness (Hepatitis)
- swelling of lymph glands
- your acne may get worse at the beginning of treatment. However, this should improve as you continue treatment
- increased skin pigmentation
- skin inflamed, swollen and darker than usual, especially at the face
- increased sensitivity to the sun during treatment
- excessive sweating
- bacterial infections
- bacterial infections at the base of the nails, with swelling, redness or a discharge of pus
- nail changes
- increased body hair
- changes in the texture of your hair, thickening of the hair. Your hair should become normal again when treatment is over
- poor night vision. This can happen quite suddenly
- changes in colour vision
- intense eye irritation, swelling of the cornea (keratitis) and cloudy surface of the eye (cataracts)
- irritation while wearing contact lenses
- abnormal sensitivity of light. You may need sunglasses to protect your eyes from being dazzled
- inflammation of blood vessels (sometimes with bruising, red patches)
- dizziness, drowsiness
- convulsions or seizures
- Diabetes (causing increased level of blood glucose with thirst and increased urination)
- blurred vision, difficulty seeing, headaches and even a loss of vision
- severe acne
- a rash or abnormal reddening on the face
- widespread rash
- small, dull, red skin growths in the mouth and nose.
- arthritis, bone changes (for example, delayed growth, changes to bone density, abnormal bone growths)
- swelling of tendons and ligaments. Symptoms include stiffness, swelling, ache, pain of the joint.
- calcium deposits in soft tissue
- inflammation of the pancreas

If you experience pain in your joints or muscles, reduce the amount of physical activity and exercise you do during your treatment.

If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE ISOTRETINOIN

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the box. This is given after the letters EXP. The expiry date refers to the last day of that month.
Do not store above 25°C. Store in the original packaging.

When you have finished your treatment, you must return all the remaining capsules to your pharmacist. Do not dispose yourself via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Isotretinoin 5 mg, 10 mg, 20 mg, 40 mg Soft Capsule contains - The active substance is:

For a soft capsule of 5 mg: isotretinoin 5 mg
For a soft capsule of 10 mg: isotretinoin 10 mg
For a soft capsule of 20 mg: isotretinoin 20 mg.
For a soft capsule of 40 mg: isotretinoin 40 mg.

The other ingredients are: soya-bean oil, hydrogenated vegetable oil and beeswax yellow.

Composition of the capsule shell of 5 mg, 20 mg and 40 mg: gelatin, glycerol, purified water, red iron oxide (E172), yellow iron oxide (E172), and titanium dioxide (E171).
Composition of the capsule shell of 10 mg: gelatin, glycerol, purified water, and red iron oxide (E172).

What Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsule looks like and contents of the pack -
Each Isotretinoin 5 mg Soft capsule, has a bi-coloured opaque red/brown and cream gelatin shell, with a bright yellow/orange fill. The oval capsule is printed on one side in black ink with the logo “5”. Each Isotretinoin 10 mg Soft Capsule, has a red/brown gelatin shell, with a bright yellow/orange fill. The oval capsule is printed on one side in black ink with the logo “10”. Each Isotretinoin 20 mg Soft Capsule, has a bi-coloured opaque red/brown and cream gelatin shell, with a bright yellow/orange fill. The oval capsule is printed on one side in black ink with the logo “1 20”.
Each Isotretinoin 40 mg Soft Capsule, has an opaque orange/brown gelatin shell, with a bright yellow/orange fill. The oval capsule is printed on one side in black ink with the logo “1 40”.
There are 30 capsules in each box.

Marketing Authorisation Holder and Manufacturer -

Marketing Authorisation Holder: Jenson Pharmaceutical Services Ltd, Carradine House, 237 Regents Park Road, London, N3 3LF

Manufacturer: Catalent France Beinheim S.A., 74 rue Principale, 67930 Beinheim, France.

This leaflet was last approved on {08/2011}. 
Module 4

Labelling – text versions

The MAH has submitted text versions only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. The labelling texts are identical apart from the strength and PL number.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING |
| [NATURE/TYPE] |

1. **NAME OF THE MEDICINAL PRODUCT**

Isotretinoin 5/10/20/40 mg Soft Capsules

Isotretinoin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each soft capsule contains 5/10/20/40 mg of Isotretinoin

3. **LIST OF EXCIPIENTS**

Contains soya-bean oil. See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

Soft capsule

30 capsules

50 capsules

100 capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral

Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Warning for Female Patients

Isotretinoin will damage an unborn baby. You must not take Isotretinoin if you are pregnant or there is any possibility that you could be pregnant. You must use effective birth control for one month before treatment, during treatment and for one month after treatment ends.
8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original packaging to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

When you have finished your treatment, return all the unused capsules to your pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
237 Regents Park Road,
London,
N3 3LF
UK

Tel: +44 (0) 20 8346 5588
fax: +44 (0) 20 8346 5599
e-mail: info@jensongroup.com

12. MARKETING AUTHORISATION NUMBER(S)

PL 17871/0100/0101/0102/0103

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Prescription only medicine

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

{name} {strength}
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Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Jenson Pharmaceutical Services Ltd Marketing Authorisations for the medicinal products Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules (PL 17871/0100-3; UK/H/3577/001-4/DC) on 13th September 2011. The products are prescription-only medicines.

These are abridged applications for Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules, submitted under Article 10.1 of 2001/83 EC, as amended, for the 5 mg, 10 mg and 20 mg products, and under Article 10.3 of 2001/83 EC, as amended, for the 40 mg product. The applications refer to the UK originator products, Roaccutane 5 mg, 10 mg and 20 mg soft capsules (PL 00031/0158, 0159 and 0160), licensed to Roche Products Limited on 30th June 1983, 31st March 1993 and 30th June 1983, respectively. The UK reference products have been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired. The innovator does not market a 40 mg strength capsule. Therefore, the application for the 40mg strength capsules was submitted as a hybrid application making reference to Roaccutane 5mg, 10mg and 20mg soft capsules. The use of Article 10.3 is accepted, given that the reference products allow single doses of 40mg (as 1mg/kg).

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, Jenson Pharmaceutical Services Ltd applied for Marketing Authorisations for Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules in Belgium, Italy, Poland, Portugal and Spain. Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules are indicated for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

Hypercornification of the epithelial lining of the pilosebaceous unit leads to shedding of corneocytes into the duct and blockage by keratin and excess sebum. This is followed by formation of a comedone and, eventually, inflammatory lesions. Isotretinoin inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly programme of differentiation. Sebum is a major substrate for the growth of Propionibacterium acnes so that reduced sebum production inhibits bacterial colonisation of the duct.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that these are generic and hybrid applications, cross-referring to products that have been licensed for over 10 years.

The applications are supported by two bioequivalence studies presented by the applicant – one study compares 2x20 mg capsules of the test and reference products, in support of the 5, 10 and 20 mg strength applications; the second study compares the 40 mg test product with
2x20 mg of the reference product. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP). They are described in the ‘Clinical aspects’ section.

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The applications include an adequate Risk Management Plan (RMP) The MAH proposes appropriate risk-minimisation measures, in addition to routine pharmacovigilance activities, in order to minimise the identified risks.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). There is no reason to conclude that marketing of these products will change the overall use pattern of the existing market and it will not result in an increased environmental exposure to the active substance. There are no environmental concerns associated with the method of manufacture or formulation of the products.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Isotretinoin 5 mg Soft Capsules  
Isotretinoin 10 mg Soft Capsules  
Isotretinoin 20 mg Soft Capsules  
Isotretinoin 40 mg Soft Capsules |
| Name(s) of the active substance(s) (INN) | Isotretinoin |
| Pharmacotherapeutic classification (ATC code) | Retinoid for the treatment of acne (D10BA01) |
| Pharmaceutical form and strength(s) | Soft capsules  
5 mg, 10 mg, 20 mg, 40 mg |
| Reference numbers for the Decentralised Procedure | UK/H/3577/001-4/DC |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/3577/001 & 004/DC: BE, ES, IT, PL, PT  
UK/H/3577/002 & 003/DC: BE, IT, PL |
| Marketing Authorisation Number(s) | PL 17871/0100-3 |
| Name and address of the authorisation holder | Jenson Pharmaceutical Services Ltd  
Carradine House  
237 Regents Park Road  
London  
N3 3LF |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Isotretinoin

Nomenclature:

INN: Isotretinoin
Chemical names: (2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid

Structure:

Molecular formula: C\textsubscript{20}H\textsubscript{28}O\textsubscript{2}
Molecular weight: 300.4 g/mol
CAS No: 4759-48-2
Physical form: A yellow or light-orange, crystalline powder
Solubility: Soluble in methylene chloride, slightly soluble in alcohol

The active substance, isotretinoin, is the subject of a European Pharmacopeia (Ph. Eur) monograph.

All aspects of the manufacture and control of isotretinoin are supported by European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of isotretinoin for inclusion in these medicinal products.

The Certificate of Suitability specifies that the retest period of the active substance is 36 months, when stored in polythene (PE) bags, within aluminium cans.
MEDICINAL PRODUCT

Description and Composition

Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules are presented as soft, oval capsules with specified markings. Full descriptions of the individual capsules may be found by referring to the SmPCs or patient information leaflet text. The capsules contain an oily suspension containing 5 mg, 10 mg, 20 mg or 40 mg of the active ingredient, isotretinoin.

Other ingredients consist of pharmaceutical excipients, namely glycerol, gelatin, purified water, red iron oxide (E172), lecithin and medium chain triglycerides making up the capsule shells; refined soya-bean oil, yellow beeswax and hydrogenated vegetable oil (derived from soya-bean oil) making up the capsule contents; purified water and ethanol making up the ‘ribbon print solvent’; and SDA 35 alcohol, propylene glycol, black iron oxide, polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol/PEG 400 and ammonium hydroxide making up the black printing ink. The 5 mg, 20 mg and 40 mg strength capsules (PL 17871/0100, 0102, 0103) additionally contain yellow iron oxide (E172) and titanium dioxide (E171) in the capsule shells. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph. Eur monographs, with the exceptions of hydrogenated vegetable oil and black printing ink, which are controlled to satisfactory in-house specifications; and the colourants, yellow iron oxide (E172), red iron oxide (E172) and titanium dioxide (E171), which comply with the EU food colouring regulation 95/45/EC. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is gelatin. Satisfactory documentation has been provided by the gelatin suppliers stating that the gelatin they provide complies with the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, capsule formulations, similar to the innovator Roaccutane products, containing 5 mg, 10 mg, 20 mg or 40 mg of isotretinoin.

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process.
Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The medicinal products are licensed for marketing in opaque, white, triplex laminate, thermoform blisters comprised of polyvinylchloride (PVC), polyvinylidene chloride (PVdC) and polyethylene (PE). The blister strips are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 30, 50 or 100 capsules. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-lives of 30 months, for the 5 mg strength capsules, and 3 years for the 10 mg, 20 mg and 40 mg strength capsules. Storage instructions are ‘Do not store above 25°C. Store in the original container. Keep the container tightly closed to protect from light’.

Quality Overall Summary

A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summaries of Product Characteristics (SmPCs), and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The MAH has submitted text versions of the PIL and labelling only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. The labelling texts fulfil the statutory requirements for Braille. The user testing of the PIL text has been evaluated and is accepted.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are generic and hybrid applications, cross-referring to products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of isotretinoin, a widely used and well-known active substance. The overview, dated November 2009, cites 28 references from the published literature dated up to 2007. The CV of the non-clinical expert has been supplied. For applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator medicinal products, Roaccutane 5 mg, 10 mg and 20 mg soft capsules (Roche Products Limited).

There are no objections to approval of Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules are indicated for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

The indications are identical to those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

The toxicology of isotretinoin is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of isotretinoin is well-known. With the exception of the bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics – bioequivalence study

The applications are supported by two bioequivalence studies presented by the applicant. One study compares 2x20 mg capsules of the test and reference products - Isotretinoin 20 mg Soft Capsules and Roaccutane 20 mg, soft capsule (Roche, France) - in support of the 5, 10 and 20 mg strength applications. The second study compares the 40 mg test product (Isotretinoin 40 mg Soft Capsules) with 2x20 mg of the reference product (Roaccutane 20 mg, soft capsule). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products. The UK reference product, Roaccutane 20mg soft capsules, is considered to be equivalent to the clinical reference product, Roaccutane 20 mg, soft capsule (Roche, France).

The primary pharmacokinetic parameters for the studies were $C_{\text{max}}$, $AUC_{0-1}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$, $AUC_{0-1}$, and $AUC_{0-\infty}$ for isotretinoin and its major metabolite, 4-oxo isotretinoin.
**Study A – 20 mg strength**

This was a randomised, two-way, two-period, single-dose crossover bioequivalence study conducted in 36 healthy adult human male subjects under fed conditions. It is considered reasonable to study fed subjects as the SmPCs state that the products should be taken with food. The volunteers were randomised to receive a dose of 40 mg (2 x 20 mg) of either the applicant’s test product or the reference product isotretinoin capsule formulations. A satisfactory washout period of 2 weeks was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 144.0 hours after administration of test or reference product. Plasma levels of isotretinoin and 4-oxo isotretinoin were detected by a validated HPLC analytical method.

**Results:**

36 subjects were enrolled in the study; all 36 completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

*Safety –* There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for isotretinoin and 4-oxo isotretinoin for a randomised, two-period, two-treatment, single-dose crossover study; n=36 healthy subjects, dosed fed; t=144 hours; washout period: 2 weeks

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ratio of Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isotretinoin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>1.05</td>
<td>94-118%</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng.h/ml)</td>
<td>1.08</td>
<td>101-117%</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.h/ml)</td>
<td>1.09</td>
<td>101-117%</td>
</tr>
<tr>
<td><strong>4-oxo isotretinoin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>1.13</td>
<td>102-126%</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng.h/ml)</td>
<td>1.11</td>
<td>101-122%</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.h/ml)</td>
<td>1.07</td>
<td>97-117%</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum plasma concentration  
$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours  
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

**Conclusion**

The results of the bioequivalence study show that the 20 mg strength test and reference products are bioequivalent, under fed conditions, as the confidence intervals for $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80-125%, in line with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CPMP/EWP/QWP/1401/98). The only parameter falling outside the standard 0.8-1.25 range is the $C_{\text{max}}$ for the metabolite, which is acceptable.
Study B – 40 mg strength

This was a randomised, single-dose crossover bioequivalence study conducted in 36 healthy adult human male subjects under fed conditions. It is considered reasonable to study fed subjects as the SmPCs state that the products should be taken with food. The volunteers were randomised to receive a dose of 40 mg of either the applicant’s test product (Isotretinoin 40 mg Soft Capsules) or the reference product (Roaccutane 20 mg, soft capsule – 2 x 20 mg) isotretinoin capsule formulations. A satisfactory washout period of 3 weeks was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 7 days after administration of test or reference product. Plasma levels of isotretinoin and 4-oxo isotretinoin were detected by a validated HPLC analytical method.

Results:

36 subjects were enrolled in the study; all 36 completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety – There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for isotretinoin and 4-oxo isotretinoin for a randomised, single-dose crossover study; n=36 healthy subjects, dosed fed; t=7 days; washout period: 3 weeks

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ratio of Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
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<tr>
<td><strong>Isotretinoin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>1.06</td>
<td>93-120%</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.h/ml)</td>
<td>0.99</td>
<td>91-109%</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng.h/ml)</td>
<td>1.00</td>
<td>91-108%</td>
</tr>
<tr>
<td><strong>4-oxo isotretinoin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>0.95</td>
<td>86-106%</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.h/ml)</td>
<td>0.96</td>
<td>87-106%</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng.h/ml)</td>
<td>0.95</td>
<td>86-105%</td>
</tr>
</tbody>
</table>

\( C_{\text{max}} \) maximum plasma concentration

\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to \( t \) hours

\( \text{AUC}_{0-\infty} \) area under the plasma concentration-time curve from time zero to infinity

Conclusion

The results of the bioequivalence study show that the test product, Isotretinoin 40 mg Soft Capsules, and reference product, Roaccutane 20 mg, soft capsule – 2 x 20 mg, are bioequivalent, under fed conditions, as the confidence intervals for \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \) fall within the acceptance criteria ranges of 80-125%, in line with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CPMP/EWP/QWP/1401/98).
Discussion on Bioequivalence

Satisfactory justification is provided for a bio-waiver for Isotretinoin 5 mg and 10 mg Soft Capsules. As Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules meet the criteria specified in the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence studies on the 20 mg and 40 mg strengths can be extrapolated to the 5 mg and 10 mg strength capsules.

Clinical efficacy

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of isotretinoin is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of isotretinoin is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those of the innovator products, and are acceptable.

Patient Information Leaflet

The final PIL text is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling text is satisfactory.

Clinical overview

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The overview, dated October 2009, cites 84 references from the published literature dated up to year 2009. The CV of the clinical expert has been supplied.

CONCLUSIONS

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Isotretinoin 20 mg Soft Capsules and the reference product, Roaccutane 20 mg, soft capsule (Roche, France); and between the applicant’s Isotretinoin 40 mg Soft Capsules and the reference product, 2 x Roaccutane 20 mg, soft capsule (Roche, France). The UK reference product, Roaccutane 20mg soft capsules, is considered to be equivalent to the clinical reference product, Roaccutane 20 mg, soft capsule (Roche, France).

As the proposed products, Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules, meet the criteria specified in the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence studies on the 20 mg and 40 mg strengths were extrapolated to the 5 mg and 10 mg strength capsules, and omission of further bioequivalence studies on the lower strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those of the innovator products and are satisfactory.

The final PIL text is in line with the SmPCs and is satisfactory. User-testing of the PIL text has been accepted based on bridging to the successful user-testing of the PIL for Isotretinoin 5 mg, 10 mg and 20 mg Soft Capsules (UK/H/0504/001-3/II/023/MR). The text, content and layout of the proposed PIL are similar to the approved PIL for the stated products. The bridging is accepted.

The approved labelling texts are satisfactory and fulfil the statutory requirements for Braille.

The MAH has submitted text versions only for the PIL and labelling and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies and their conclusions support the claim that the applicant’s Isotretinoin 5 mg, 10 mg, 20 mg and 40 mg Soft Capsules are therapeutically equivalent to the innovator products, Roaccutane 5 mg, 10 mg and 20 mg soft capsules (Roche Products Limited). Extensive clinical experience with isotretinoin is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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